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To: Pharmacosmos A/S

From: Professor Klaus Bock, Carlsberg Laboratory

Date: 6<sup>th</sup> February 2004

Subject: Assessment of the carbohydrate structural identity of dextran derived compounds produced by two different chemical oxidation approaches as written in US patent 4,370,476, Usher et al. (Pat. I) and patent application WO 00/30657, Andreassen et al. (Pat. II) based on literature studies.

As carbohydrate chemists with special expertise on carbohydrate structural assignment (see enclosed c.v.) I have the following comments to the carbohydrate structures produced by the methods described in the above-mentioned two documents.

Pat. I: The method described by Usher et al. is a traditional carbohydrate chemistry reaction for (partial) degradation for carbohydrate structures: the periodate oxidation (see Ref. 1). The virtue of this reaction is a break down of the cyclic (five or six-membered-rings) or open chain structure of carbohydrates with resulting poly-aldehydes. These have in the Pat. I description been chemically modified in several ways (oxidation, (Br<sub>2</sub>)), cyanohydrin (HCN), chain elongation to acids or to carboxylic acids all with the purpose to produce compounds with at least two carboxylic acid substituents (but generally many more along the modified polymeric chain).

In addition to the multivalent substitution pattern, the overall structure of the product is modified extensively because several of the six-membered-rings have been destroyed and replaced by two-carbohydrate acid residues. The structure is much more like a linear polymer without a well-defined conformation.

Pat. II: The method described in Pat. II by Andreassen et al. is based on a different chemical approach, where the carbohydrate polymer according to Ref. 2 is left virtually unchanged but aim only at modification at the reducing end of the dextran chain. After partial reduction of the terminal hemi-acetal the remaining hemi-acetals are oxidized to carboxylic acids by standard hypochlorite oxidation (see Ref. 3a and 3b).

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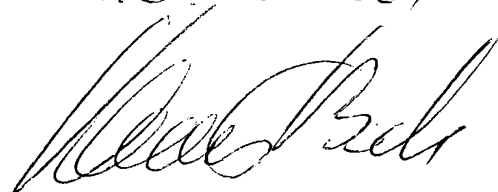
The methods used for the evaluation can (in smaller amounts) also produce compounds with carboxylic acids at the 6-position of the 1-3 branching hexopyranoses, but oxidation will predominantly take place at the more relative reducing end hemi-acetal.

The overall conformation of this product will be completely different from the product produced by Pat. I, because none of the six mentioned rings are destroyed by the methods described in Pat. II (see Ref. 2).

However, oxidation by sodium hypochlorite in basic media can be strongly dependent on the reaction conditions as described in Ref. 4, where these reaction conditions are described to produce compounds similar to the periodate oxidation reaction followed by Br<sub>2</sub> oxidation as mentioned above in Pat. I

### Conclusion

The carbohydrate structures produced by the two patens can be completely different or very similar dependent on the specific reaction conditions. A experimental study on the reaction compounds produced by the Pharmacosmos method will therefore be required to substantiate the structural identity with certainty and thus to be used as final documentation in the material to be presented to the patent examiner, as also suggested in the correspondence with him.

10. 2. 2004  


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# CARLSBERG LABORATORY DEPARTMENT OF CHEMISTRY

Professor Klaus Bock

## Curriculum Vitae, Klaus Bock 10-02-04



Name: Klaus Bock  
Rank: Professor  
Place of Birth: Copenhagen, Denmark  
Date of Birth: July 2, 1944  
Citizenship: Danish  
Married  
Sex: Male  
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### Education:

M.Sc. in Civilengineering (Chemistry) 1968.

Ph.D (Lic.techn.) in Organic Chemistry 1970 The Technical University of Denmark with Professor Chr. Pedersen "Reactions of Unsaturated Sugars with Hydrogen Halides".

### Employments:

- a) 1970-1972 Assistant Professor, Department of Organic Chemistry, Technical University of Denmark, DK-2800 Lyngby, Denmark
- b) 1972-1988 Associate Professor (Lecturer) Department of Organic Chemistry, Technical University of Denmark DK-2800 Lyngby, Denmark
- c) 1974-1975 Visiting Associate Professor, Department of Chemistry, U.B.C. Vancouver, B.C. Canada
- d) 1977 Sep. Visiting Associate Professor, Department of Chemistry, University of Hamburg, Hamburg, Germany Invited by DAAD (Deutscher Akademischer Austauschdienst)
- e) 1979 Visiting Professor, Centre de Recherches sur le Macromolecules Vegetales, Universite de Grenoble, Grenoble, France. Invited by: Centre National de la Recherche Scientifique (june-July)
- f) 1979, May Visiting Professor, Department of Chemistry University of Alberta, Edmonton, Canada
- g) 1981 Alberta Heritage Foundation for Medical Research, Visiting Scientist, Department Chemistry, University of Alberta, Canada (May- July)
- h) 1982 Visiting Scientist National Research Council Canada, Division of Biological Sciences, Ottawa, Canada (August)
- i) 1984 Visiting Scientist National Research Council Canada, Division of Biological Sciences, Ottawa, Canada (March)
- j) 1988 Sep- Professor, Head of Chemistry Department, Carlsberg Laboratory, Valby, Copenhagen Denmark
- k) 1993-99 Research Director, Carlsberg Research Center
- l) 1999 Jan- Group Vice President for Research, Carlsberg A/S
- m) 2001, Mar- Executive Vice President, Carlsberg A/S

### Awards:

- 1979: Ole Roemer, Research Award
- 1986: International Carbohydrate Award in Honor of Roy L. Whistler
- 1992: Alexander von Humboldt Research Award
- 1994: Bjerrum, Brønsted, Lang Lecture, Royal Danish Academy of Sciences and Letters
- 2000: Danish Natural Science Academy, Industrial Award.

### Memberships:

- Member of Danmarks Naturvidenskabelige Akademi (DNA) 1982-
- Member of Danish Academy of Technical Sciences (ATV) 1989-

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# CARLSBERG LABORATORY DEPARTMENT OF CHEMISTRY

Professor Klaus Bock

- Member of The Royal Danish Academy of Sciences and Letters, 1990-
- Fellow of The Royal Society of Chemistry (London), 1991-

## Research:

Have published 260 papers in international journals with referee within the area of analytical and synthetic carbohydrate chemistry with special emphasis of the application of NMR spectroscopy in structural studies of carbohydrate derivatives and their interaction with enzymes. Recent interests have focused on protein-carbohydrate interactions, particularly the synthesis and structural analysis of glycopeptides.

## International Committees:

- August 1986-2000, Chairman for the Board of Overseers for the Organization behind CARBBANK, a structural database for complex carbohydrate structures.
- 1992-95 Member of the Advisory Panel for Collaborative Research Grants Programme of NATO, Bruxelles. Member of the International Scientific Advisory Board of the Bijvoet School for Biomolecular Chemistry. (1996-2003)
- Since November, 1996 Member of the Board of Directors for the Swedish Foundation for Strategic Research (SSF) programme "Glycoconjugates in Biological Systems (GLIBS)"

## On the Editorial Board of the following International Journals:

- Journal of Carbohydrate Chemistry (since July 1983)
- Glycoconjugate Journal (since July 1985- 2002)
- Carbohydrate Research (October 1986-1998)
- Carbohydrate Letters (since 1993)

## Danish Memberships:

- Member of the Board of T. Holm's Foundation (1986-)
- Chairman of the Kaj Linderstrøm Lang's Gold Medal Foundation. (1988-)
- Member of the Board of The Emil Chr. Hansen's Foundation (1988-)
- Member of the Board of Governors Nørre Gymnasium, (1992-98)
- Member of The Danish Academy of Technical Sciences, Industrial Research Fellowship Committee (1993-1999)
- Member of the Board of Trustees of A. Tovborg Jensen's Foundation (1994-)
- Member of the Board of Pharmexa A/S (1997-), Deputy chairman from august 2000-
- Member of the Steering Group of "NeuroScience. A Drug Research Centre" (1997-2001)
- Head of the Danish National Instrument Center for NMR Spectroscopy of Biological Macromolecules 800 MHz facility at Carlsberg Laboratory (1997-
- Member of the Advisory Research Committee for the Danish Ministry of Food and Agriculture. (1998-2000)
- Member of the Board of Trustees of BRIC (Biotechnological Research and Innovation Center) appointed as personal member by the Minister of Research (2000-
- Member of the Industrial Committee of the Centre for Advanced Food Studies (2000-
- Chairman of the Board of Directors of Combio A/S, (july 2000-
- Member of the Board of Trustees of The Carlsberg Bequest to the Memory of Brewer J.C. Jacobsen, (sept. 2001-
- Member of the Board of Directors of VersaMatrix A/S, (sept. 2002-
- Member of the Board of Directors of Alfred Jorgensen Laboratory, (sept. 2002-2003)
- Member of the Board of Directors of the iNANO Center at Aarhus University, (june 2003-

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# Analytical Chemistry of Carbohydrates

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Georg Thieme Verlag Stuttgart • New York 1998

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